REMARKS

The specification has been amended to capitalize trademarks and remove reference to embedded hyperlinks.

Applicants have cancelled Claims 1-3, 7-10 and 15 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claims 4, 5, 6 and 14 to delete elements (a)-(d). Claims 4 and 5 are amended to include the limitation "wherein said nucleic acid is more highly expressed in esophageal tumor tissue compared to normal esophageal tissue." Claims 11 and 12 are amended to remove informalities. Claim 14 is amended to indicate that the isolated nucleic acid hybridizes under stringent conditions, and recites the stringent conditions. Claim 14 also is amended to include "or a complement thereof" to amended elements (a)-(c), and the following text "wherein said isolated nucleic acid molecule is suitable for use as a PCR primer, or probe; and wherein said isolated nucleic acid is at least about 20 nucleotides in length." Claim 16 is amended to read "at least about 50 nucleotides in length." Claim 17 is amended to depend from Claim 4. Claim 19 is amended to indicate that the cell is an isolated cell. New Claims 21-31 have been added.

Applicants submit that no new matter has been added by the amendments, and that support for the amendments can be found throughout the specification. For example, support for the amendment to Claims 4 and 5 regarding differential expression in esophageal tumor can be found in Example 18 beginning at paragraph [0529], as well as paragraph [0336] of the specification. Support for the amendments to Claim 14 can be found, for example, at paragraphs [0012], [0317], and [0327] of the specification. Support for the amendment to Claim 16 and new Claims 21-25 can be found, for example, at paragraph [0012]. Support for new Claims 26-31 can be found, for example, in the claims as originally filed, and paragraphs [0227] and [0317].

Claims 4-6, 11-14, and 16-31 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed February 8, 2005. For the reasons set forth below, Applicants respectfully traverse.

Correction of Inventorship under 37 CFR §1.48(b)

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Rejection under 35 U.S.C. §101 – Utility

The PTO has rejected Claims 1-20 as lacking a specific, substantial, and credible utility. The PTO argues that utilities asserted in the specification are not specific and substantial or well established. One of the asserted utilities for the claimed nucleic acids is use as a diagnostic tool, as well as therapeutically as a target for treatment, based on the data that PRO1315 cDNA is more highly expressed in esophageal tumor as compared to normal esophagus tissue.

The PTO recognizes this as a "possible utility," however, the PTO asserts that there is no guidance on how to use this information, that no absolute or relative levels are disclosed, that the significance of the result is not known, and that the information is too sparse to allow the encoding polynucleotide to be used as a diagnostic marker for esophageal tumor. The PTO argues that more specifics about necessary sample size, expression level range for normal and tumor tissue, and "other factors", the specification has not provided the invention in a form readily usable by the skilled artisan such that significant further experimentation is unnecessary.

The PTO cites Hu *et al.* (J. Proteome Res., 2(4):405-12 (2003)) to support its assertion that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue, and that more information regarding expression level of the nucleic acid is needed.

The PTO also argues that even if the polynucleotide has utility as a tumor marker, there is no such utility for the polypeptide because there is no reason to suspect that there is an alteration in the amount of the polypeptide in esophageal tumor versus normal tissue. For the above reasons, the PTO asserts that there is no substantial and specific utility for the nucleic acid of SEQ ID NO:75.

Applicants respectfully disagree and submit that for the reasons stated below, the claimed nucleic acids have a credible, substantial, and specific utility.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "to violate § 101 the claimed device must be totally incapable of achieving a useful result." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed.Cir.1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular

practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., 'question') the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained [] because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**. M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted

> utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

Thus, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed nucleic acids have utility as diagnostic tools for cancer, particularly esophageal cancer. Applicants' asserted utility rests on the following argument:

1. Applicants assert they have provided reliable evidence that mRNA for the PRO1315 polypeptide is expressed at least two-fold higher in esophageal tumor compared to normal esophageal tissue, and therefore the claimed nucleic acids are useful as diagnostic tools. Applicants are not asserting that the claimed nucleic acids will necessarily provide a definitive diagnosis of cancer, but rather that they are useful, alone or in combination with other diagnostic tools to assist in the diagnosis of certain cancers.

2. Applicants submit that it is not necessary to know what role the PRO1315 gene plays in cancer to use its differential expression as a diagnostic tool.

3. It is not required to prove that the PRO1315 polypeptide is also differentially expressed in certain tumors to establish the utility of the claimed nucleic acids.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO has challenged the reliability of the evidence reported in Example 18, and states that it does not provide the expression levels, and that the information is too sparse to allow the encoding polynucleotide to be used as a diagnostic marker for tumors;

2. The PTO cites Hu *et al.* for the assertion that the literature cautions against drawing conclusions based on small changes in transcript expression levels;

3 The PTO asserts that the nucleic acid cannot derive utility from the encoded polypeptide because there is no known physiological or clinical significance of the polypeptide

and because there is no reason to think that there is alteration of encoded polypeptide in esophageal tumor relative to normal esophageal tissue.

As detailed below, Applicants submit that the PTO has failed to demonstrate that this is one of the "rare cases" where the applicants have "asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." M.P.E.P. § 2107.02 III B. First, Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, (attached as Exhibit 1) which establishes the reliability of the data of Example 18. Second, the reference cited by the PTO is not contrary to Applicants' arguments and evidence, and therefore is not evidence to support the PTO's position. Third, Applicants submit that given the well-established correlation between a change in the level of mRNA with a corresponding change in the levels of the encoded protein, the PRO1315 protein is likely differentially expressed in esophageal tumors. However, utility for the pending claims does not rely on whether the encoded polypeptide is overexpressed, and as such whether or not increased levels of PRO1315 mRNA correlate with increased levels of PRO1315 protein is not presently an issue.

Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute or statistical certainty.**

Applicants have established that the Gene Encoding the PRO1315 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue and is Useful as a Diagnostic Tool

Applicants first address the PTO's argument that the evidence of differential expression of the gene encoding the PRO1315 polypeptide in certain tumors compared to their normal counterparts is insufficient because the specification provides no information regarding values of the differences in transcript levels, and the disclosure of the specification is too sparse. Applicants also address the PTO's argument that the data do not establish a utility because the specification does not disclose any information on the level of expression, activity, or role of the PRO1315 polypeptide in cancer. Applicants submit that the gene expression data provided in

Example 18 of the present application are sufficient to establish a specific and substantial utility for the claimed nucleic acids related to the gene encoding the PRO1315 polypeptide.

Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (attached as Exhibit 1). In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples.

He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

Applicants submit that a lack of known role for the gene encoding PRO1315 in cancer does not prevent its use as a diagnostic tool for cancer. Whether the differential expression of the gene encoding PRO1315 is a cause or result of the esophageal tumors is irrelevant to whether its differential expression can be used to assist in diagnosis of cancer – one does not need to know why the PRO1315 gene is differentially expressed, or what the consequence of the differential expression is, in order to exploit the differential expression to distinguish tumor from normal tissue.

The PTO has recognized that the utility of a nucleic acid does not depend on the function of the encoded gene product. The Utility Examination Guidelines published on January 5, 2001

state "In addition, the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have a specific and substantial utility because, e.g. it hybridizes near a disease-associated gene or it has a gene regulating activity." (Federal Register, Volume 66, page 1095, Comment 14). While Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO issues patents relating to nucleic acids which are useful for diagnosing particular conditions regardless of whether the nucleic acids are the causative agent for the condition. For example, polymorphisms which are indicative of a predisposition to a particular condition are patentable (*see, e.g.,* U.S. Patent No. 6,465,185, U.S. Patent No. 6,228,582, and U.S. Patent No.6,162,604 submitted herewith as Exhibits 2-4), even though they may or may not cause the disease itself. Similarly, the present nucleic acids which are useful for determining whether an individual has cancer are useful regardless of whether or not they are the cause of the cancer.

The PTO relies on a single references to support its assertion that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. The PTO cites Hu *et al.* (J. Proteome Res., 2(4):405-12 (2003)) for support for the conclusion that not all genes with increased expression in cancer have a known or published role in cancer. Applicants respectfully submit that this references does not satisfy the PTO's burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility.

In Hu, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation

was only found among estrogen receptor-positive tumors, not less-prevalent ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and reflect nothing regarding the ability of a gene that is 2-fold or more differentially expressed in tumors to serve as a disease marker. Hu acknowledges the shortcomings of this method in explaining the disparity in Hu's findings for ER-negative versus ER-positive tumors: Hu attributes the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors. *Id.* Because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially-expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially-expressed genes exists. Accordingly, Hu's methodology yields results that provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease.

Applicants submit that a lack of known role for PRO1315 in cancer does not prevent its use as a diagnostic tool for cancer. There is a difference between use of a gene for distinguishing between tumor and normal tissue on the one hand, and establishing a role for the gene in cancer on the other. Genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but the genes can still show a consistent and measurable change in expression. While such genes may or may not be good targets for further research, they can nonetheless be used as diagnostic tools. Thus, Hu does not refute the Applicants' assertion that the PRO1315 gene can be used as a cancer diagnostic tool because it is differentially expressed in certain tumors.

The position of the PTO is inconsistent with the analogous standard for therapeutic utility of a compound that "the mere identification of a pharmacological activity of a compound that is

relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." M.P.E.P. §2701.01 (emphasis original). Here, the mere identification of altered expression in tumors is relevant to diagnosis of tumors, and, therefore, provides an immediate benefit to the public.

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. Hu is not sufficient to prove that a person of skill in the art would consider it unlikely that a gene differentially expressed in certain tumors can be used as a diagnostic tool since this reference does not address this issue. Given the lack of support for the PTO's position, and the supporting evidence provided by the Applicants, one of skill in the art would be more likely than not to believe that the claimed nucleic acids related to PRO1315 gene can be used as diagnostic tools for cancer, particularly esophageal cancer.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1315 cDNA between esophageal tumor tissue and normal esophageal tissue. Therefore, it follows that expression levels of the PRO1315 gene can be used to distinguish esophageal tumor tissue from normal esophageal tissue. The PTO has not offered any significant arguments or evidence to the contrary. Applicants have therefore established a utility for the claimed nucleic acids as diagnostic tools for cancer, particularly esophageal tumors.

Applicants have established that the Accepted Understanding in the Art is that there is a Positive Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Applicants have asserted that there is a direct correlation between changes in the level of mRNA and changes in the level of expression of the corresponding protein. Because the claims have been amended such that the claimed nucleic acids are not defined by the sequence of the polypeptide they encode, the question of whether there is a correlation between changes in gene expression and changes in protein expression are not presently at issue. However, Applicants submit that they have established for the record that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein. Given Applicants' evidence of differential expression of the

mRNA for the PRO1315 polypeptide in esophageal tissue, it is more likely than not that the PRO1315 polypeptide is also differentially expressed.

The PTO states that even if the claimed nucleic acid had utility, the "encoded polypeptide would have no such utility since there is no reason to suspect that there is alteration of polypeptide sequence or amount in esophageal tumor *versus* normal tissue." Office Action at 4. No substantiating evidence is presented. This statement in the Office Action does not satisfy the PTO's burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility. The PTO cites no evidence that would cast any doubt on the Applicants assertion that in general, there is a positive correlation between changes in mRNA level and changes in the encoded protein level. As stated above, the standard for establishing a use for a claimed invention is not absolute or even statistical certainty, and thus a *necessary* correlation between mRNA levels and protein levels is not required.

In further support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 5). This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 6), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in

> abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 7) and (4th ed. 2002) (submitted herewith as Exhibit 8)). Figure 9-2 of Exhibit 7 shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 7 provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 7 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Exhibit 7 at 453 (emphasis added). Thus, as established in Exhibit 7, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Exhibit 8, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Exhibit 8 at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Exhibit 8 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Exhibit 8 at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for

regulating protein expression, "[f]or most genes transcriptional controls are paramount." Exhibit 8 at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (submitted herewith as Exhibit 9) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, submitted herewith as Exhibit 10. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression." Exhibit 10 at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Exhibit 10 at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." Exhibit 10 at 7.

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted herewith as Exhibit 11, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

As discussed above, whether or not increased levels of PRO1315 mRNA correlate with increased levels of PRO1315 protein is not presently an issue. However, Applicants submit

together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein. In light of the lack of support for any argument by the PTO to the contrary, Applicants submit that they have established that it is more likely than not that one of skill in the art would believe that because the PRO1315 mRNA is expressed at a higher level in esophageal tumor compared to normal esophageal tissue, the PRO1315 polypeptide will also be expressed at a higher level in esophageal tumor compared to normal esophageal tissue.

The Claimed Nucleic Acids would have Diagnostic Utility even if there is no Direct Correlation between Gene Expression and Protein Expression

Even assuming *arguendo* that, there is no direct correlation between changes in gene expression and changes in protein expression for PRO1315, which Applicants submit is not true, nucleic acids related to a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

> In paragraph 6 of the Grimaldi Declaration, Exhibit 5, Mr. Grimaldi explains that:
>
> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 12), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin (attached as Exhibit 13). The article teaches that the HER-2/neu gene has been shown to be amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the

amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between changes in gene expression and changes in protein expression. However, even when this is not the case, a gene that is differentially expressed in cancer would still have utility. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed nucleic acids.

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

Applicants remind the PTO that the M.P.E.P. cautions that rejections for lack of utility are rarely sustained by federal courts, and that generally speaking, a utility rejection was sustained because the applicant asserted a utility "that could **only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art.**" M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added). Rather than being wholly inconsistent with contemporary knowledge in the art, Applicants' asserted utility is squarely within the teaching of leading textbooks in the field, and is supported by references and the declarations of skilled experts.

The PTO has not offered any arguments or cited any references to establish "that one of ordinary skill in the art would reasonably doubt" that a gene differentially expressed in certain tumors can be used as a diagnostic tool. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed nucleic acids can be used as diagnostic tools for cancer, particularly esophageal cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Nucleic Acids

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed nucleic acids related to PRO1315. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1315 gene in certain types of cancer cells, along with the declarations and references discussed above, provide a specific utility for the claimed nucleic acids.

As discussed above, there are significant data which show that the gene encoding the PRO1315 polypeptide is more highly expressed in esophageal tumor tissue compared to normal esophageal tissue. These data are strong evidence that the gene encoding the PRO1315 polypeptide is associated with esophageal tumors. Thus, contrary to the assertions of the PTO,

Applicants submit that they have provided evidence associating the gene encoding PRO1315 with a specific disease. The asserted utility as a diagnostic tool for cancer, particularly esophageal tumor, is a specific utility – it is not a general utility that would apply to the broad class of nucleic acids.

Conclusion

The PTO has asserted three arguments for why there is a lack of a substantial utility: (1) the data reporting that the PRO1315 gene is differentially expressed in certain tumors is not sufficient; (2) that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue; and, (3) that because there is no *necessary* correlation between gene amplification and protein expression, the claimed nucleic acids cannot be used as cancer diagnostic or therapeutic tools. Applicants have addressed each of these arguments in turn.

First, the Applicants provide a declaration stating that the data in Example 18 reporting higher expression of the PRO1315 gene in esophageal tumor tissue compared to normal esophageal tissue, are real and significant. This declaration also indicates that given the at least two-fold difference in expression levels, the claimed nucleic acids have utility as cancer diagnostic tools. Applicants have also shown that the precise level of expression and activity or role of the PRO1315 polypeptide or the gene that encodes it in cancer is irrelevant to the utility of the claimed subject matter. Resolution of these issues is not required to use the claimed nucleic acids as tumor diagnostic tools – one does not have to know why the PRO1315 gene is differentially expressed in certain tumors to use it as a tumor marker.

Second, Applicants have shown that the Hu reference cited by the PTO does not teach that genes differentially expressed in cancer cannot be used as diagnostic tools as the reference does not address this issue.

Third, Applicants assert that whether the encoded polypeptide is also differentially expressed in certain tumors is currently not at issue in this application. However, Applicants believe that they have established that there is a reasonable correlation between changes in gene expression and corresponding changes in the level of the encoded protein. The PTO provides no evidence to the contrary. Applicants have presented the declarations of two experts in the field along with supporting references which establish that the general, accepted view of those of skill

in the art is that there is a direct correlation between changes in mRNA levels and the encoded protein levels.

Finally, the PTO asserts that there is no asserted specific utility. Applicants have pointed out that the substantial utilities described above are specific to the claimed nucleic acids because the gene encoding PRO1315 is differentially expressed in certain cancer cells compared to the corresponding normal cells. This is not a general utility that would apply to the broad class of nucleic acids.

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed nucleic acids as a diagnostic agent. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed nucleic acids relating to PRO1315 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO rejected Claims 1-20 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO argues that because the claimed invention is not supported by a substantial, specific and credible utility, the claims are not enabled. The PTO

states that the specification does not provide sufficient guidance or working examples to be able to use the claimed nucleic acids diagnostically or therapeutically, without undue experimentation.

Applicants respectfully traverse.

As an initial matter, Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed nucleic acids. Applicants therefore request that the PTO reconsider and withdraw the enablement rejection to the extent that it is based on a lack of utility for the claimed nucleic acids.

As amended, the pending claims are to nucleic acids that have at least 95% or 99% nucleic acid sequence identity to the recited sequences and is "more highly expressed in esophageal tumor tissue compared to normal esophageal tissue." Other claimed nucleic acids can hybridize to the recited sequences under stringent conditions.

Applicants submit that the claimed nucleic acids are enabled, as one of skill in the art would know how to make and use them. It is well-established in the art how to make the claimed nucleic acids which have at least 95% or 99% sequence identity to the disclosed sequences related to SEQ ID NO: 75. Likewise, Applicants have disclosed how to determine if the recited nucleic acids are differentially expressed in esophageal tumors compared to their normal counterparts (*see, e.g.,* Example 18 beginning at paragraph [0529] of the specification). Finally, it is well-known in the art how to determine if the recited nucleic acids hybridize to the disclosed sequences under the specified stringent conditions. Thus, one of skill in the art would know how to make the claimed nucleic acids.

As discussed above, Applicants submit that they have established that one of skill in the art would believe that it is more likely than not that the PRO1315 gene is differentially expressed in esophageal tumors. Given the disclosure in the specification and the level of skill in the art, a skilled artisan would know how to use the claimed nucleic acids as diagnostic tools. For example, nucleic acids which have at least 95% or 99% sequence identity to the disclosed sequences and are "more highly expressed in esophageal tumor tissue compared to normal esophageal tissue" can be used as diagnostic tools since the claimed nucleic acids are themselves differentially expressed in certain tumors. A nucleic acid which has at least 95% or 99% sequence identity to the disclosed sequences and hybridizes to the disclosed sequences under the specified stringent conditions can be used as a hybridization probe to detect the expression of the

PRO1315 gene, making it useful as a diagnostic tool. Given the skill in the art and the disclosure of how to make and use the claimed nucleic acids, Applicants request that the PTO reconsider and withdraw its rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO has rejected Claims 1-6, 9, 10 and 14-20 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention. According to the PTO, because the claims do not require that the claimed nucleic acids or encoded polypeptides possess any particular biological activity, particular conserved structure, or other disclosed distinguishing feature, the claims fail the written description requirement. The PTO states that the claims are drawn to a genus of nucleic acids that is defined only by sequence identity. Finally, the PTO states that the only factor present in the claim is a partial structure in the form of a recitation of percent identity. The PTO concludes that in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 U.S.P.Q. 1089, 1096 (Fed. Cir. 1983); *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. *See e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains. The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

The subject matter of the pending claims concerns nucleic acids having 95% or 99% sequence identity to the nucleic acid sequence of SEQ ID NO:75, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:75, or the full-length coding sequence of the cDNA deposited under ATCC accession number 203247, with the functional recitation as amended: "wherein said nucleic acid is more highly expressed in esophageal tumor tissue compared to normal esophageal tissue." Other claimed nucleic acids hybridize to the nucleic acid sequence of SEQ ID NO:75, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:75, the full-length coding sequence of the cDNA deposited under ATCC accession number 203247, or the complements thereof, under the specified stringent conditions. We turn first to the claims which recite specific high stringency hybridization conditions.

In *Enzo Biochem v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002), the Court held that functional descriptions of genetic material may satisfy the written description requirement. In so holding, the Court gave judicial notice to the USPTO's Manual of Patent Examining Procedure, which provides that the written description requirement may be satisfied when the disclosure provides sufficiently detailed identifying characteristics, such as "complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics." *Id.* at 964, quoting 66 Fed. Reg. at 1106 (emphasis in original). In *Enzo*, the Court found describing nucleic acids based on their ability to hybridize to another nucleic acid sequence which was adequately described may be an adequate description of the nucleic acid.

This is because the hybridization function of a nucleic acid is dependent on the sequences of the nucleic acid – a disclosed function which is coupled with a known correlation between function and structure. The Court favorably discussed the PTO's example wherein "genus claims to nucleic acids based on their hybridization properties...may be adequately described if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." *Id.* at 967 (citing *Application of [Written Description] Guidelines*, Example 9) (emphasis added).

Applicants submit that the stringent hybridization conditions specified in the pending claims, alone or in combination with the recited percent sequence identity, result in all species within the genus being structurally similar. As the *Enzo* Court noted, Examples 9 and 10 of the Application of Written Description Guidelines (hereinafter "Guidelines") make clear that specifying hybridization under highly stringent conditions yields "structurally similar DNAs." Guidelines, Example 9 at page 36. The analysis of a genus claim in Example 10 of the Guidelines states:

> [T]urning to the genus analysis, the art indicates that *there is no substantial variation within the [claimed] genus because of the stringency of hybridization conditions which yields structurally similar molecules.* The single disclosed species is representative of the genus because reduction to practice of this species, considered along with the defined hybridization conditions and the level of skill and knowledge in the art, are sufficient to allow the skilled artisan to recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus. Guidelines, Example 10 at page 39 (emphasis added).

Given the level of skill in the art, specifying highly stringent conditions leads to "no substantial variation within the [claimed] genus," and therefore a skilled artisan would recognize that the Applicants were in possession of the necessary common attributes or features of the genus. This is contrary to the PTO's argument the claimed sequences do not possess "any particular conserved structure, or other disclosed distinguishing feature." Office Action at 4. The common element or attribute of the claimed genus of nucleic acids is that species of the genus contain a nucleic acid which is structurally related to SEQ ID NO: 75, such that the nucleic acids hybridize to SEQ ID NO: 75 or the related sequences under the specified high stringency conditions recited in the claims.

The present situation is not analogous to *Fiddes v. Baird*, 30 U.S.P.Q. 2d 1481, cited by the PTO. Unlike *Fiddes*, where arguably the structure of other mammalian sequences could not be conceived based on a single species of the genus, here the skill in the art is such that the sequence of nucleic acids which hybridize to SEQ ID NO: 75 under the conditions specified can be conceived. Here, the claimed genus is defined by its structure – members of the genus hybridize under the specified conditions to the specified sequences, each of which are adequately described in the specification.

Applicants submit that the pending claims relating to nucleic acids having 95% or 99% sequence identity to the nucleic acids related to SEQ ID NO:75 with the functional recitation "wherein said nucleic acid is more highly expressed in esophageal tumor tissue compared to normal esophageal tissue" are also adequately described. In Example 14 of the written description training materials, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants. Similarly, the pending claims also have very high sequence homology to the disclosed sequences and must share the same expression pattern in certain tumors. In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Similarly, in the instant application, it is well known in the art how to make nucleic acids which have at least 95% sequence identity to the disclosed sequences, and the specification discloses how to test to determine if the nucleic acid sequence is differentially expressed in esophageal tumors. Like Example 14, the genus of nucleic acids that have at least 95% or 99% sequence identity to the disclosed sequences will not have substantial variation since all of the variants must have the same expression in certain tumors.

Furthermore, while Applicants appreciate that actions taken by the PTO in other applications are not binding with respect to the examination of the present application, Applicants note that the PTO has issued many patents containing claims to variant nucleic acids or variant proteins where the applicants did not actually make such nucleic acids or proteins. Representative patents include U.S. Patent No. 6,737,522, U.S. Patent No. 6,395,306, U.S. Patent No. 6,025,156, U.S. Patent No. 6,645,499, U.S. Patent No. 6,498,235, and U.S. Patent No. 6,730,502, which are submitted herewith as Exhibits 14-19.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO: 75, by specifying the high stringency conditions under which hybridization occurs, and by describing the gene expression assay, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness

The PTO has rejected Claims 14-16 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO objects to the lack of specified stringent conditions.

Claim 15 has been canceled. Claim 14 is amended to recite specified stringent conditions for hybridization of the claimed nucleic acid. In light of these amendments, Applicants request that the PTO withdraw the indefiniteness rejections under 35 U.S.C. §112, second paragraph.

Priority Determination:

The PTO states that the earliest priority date for the instant application is the filing date, May 8, 2002. The PTO argued that the instant application and priority application Serial No. 10/006,867 do not meet the requirements of 35 U.S.C. § 112, first paragraph. However, for the reasons set forth above, the instant application and the priority application do meet the requirements of 35 U.S.C. § 112, first paragraph, and therefore, are entitled to an earlier priority date.

Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 5, 2002. The preliminary amendment states that the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/403297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. § 371 of PCT

Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 U.S.C. § 119 to U.S. Provisional Application 60/099815 filed 9/10/1998.

The sequences of SEQ ID NOs: 75 and 76 were first disclosed in U.S. Provisional Application 60/099815 filed 9/10/1998 as SEQ ID NO:1 and 2 and in Figures 1 and 2. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed nucleic acids, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. Thus, Applicants maintain that the present application is fully entitled to the benefit of at least the priority date of August 24, 2000.

Rejection under 35 U.S.C. §102(b) – Anticipation

The PTO rejects Claims 1-6, 8-10, and 14-16 as anticipated under 35 U.S.C. §102(b) by GenBank Database Accession No. AF184971. According to the PTO, AF184971 teaches a nucleic acid which is 89% identical to SEQ ID NO:75, 99.9% identical to nucleic acids 191-1743, and encodes the polypeptide of SEQ ID NO:76 lacking its associated signal peptide.

The publication date of AF184971 is January 13, 2000. The instant application claims priority to PCT/US00/23328 filed on August 24, 2000, and U.S. Provisional Application 60/099815 filed September 10, 1998. Thus, AF184971 is not available as prior art under § 102(b) since it was not published more than one year before either the August 24, 2000 or the September 10, 1998 priority date. Applicants therefore respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

Rejection under 35 U.S.C. §103(a) – Obviousness

The PTO rejects Claims 1-6 and 17-20 under 35 U.S.C. § 103(a) as being unpatentable over GenBank Database Accession No. AF184971 as applied above, and further in view of U.S. Patent No. 5,874,561. The Examiner argues that AF184971 does not teach vectors or host cells, but the '561 Patent does.

As discussed above, the publication date of AF184971 is January 13, 2000. The instant application claims priority to U.S. Provisional Application 60/099815 filed September 10, 1998, which includes the disclosure of the full length sequence of SEQ ID NOs: 75 and 76. As the September 10, 1998 date precedes the date of GenBank Database Accession No. AF184971,

January 13, 2000, Applicants have shown possession of the claimed invention prior to the publication of GenBank Database Accession No. AF184971.

The well-established "Stempel Doctrine" stands for the proposition that a patent applicant can effectively swear back of and remove a cited prior art reference by showing that he or she made that portion of the claimed invention that is disclosed in the prior art reference. (*In re Stempel*, 113 U.S.P.Q. 77 (CCPA 1957)). In other words, a patent applicant need not demonstrate that he or she made the entire claimed invention in order to remove a cited prior art reference. He or she need only demonstrate prior possession of that portion of his or her claimed invention that is disclosed in the prior art reference and nothing more.

The Stempel Doctrine was extended to cases where a reference disclosed the claimed compound but failed to disclose a sufficient utility for it in *In re Moore*, 170 U.S.P.Q. 260 (CCPA 1971). More specifically, the patent applicant (Moore) claimed a specific chemical compound called PFDC. In support of a rejection of the claim under 35 U.S.C. § 102, the Examiner cited a reference which disclosed the claimed PFDC compound, but did not disclose a utility for that compound. Applicant Moore filed a declaration under 37 C.F.R. § 1.131 demonstrating that he had made the PFDC compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. The lower court found the 131 declaration ineffective to swear back of and remove the cited reference, reasoning that since Moore had not established a utility for the PFDC compound prior to the effective date of the cited prior art reference, he had not yet completed his "invention".

On appeal, however, the CCPA reversed the lower court decision and indicated that the 131 declaration filed by Moore was sufficient to remove the cited reference. The CCPA relied on the established Stempel Doctrine to support its decision, stating:

> An applicant need **not** be required to show [in a declaration under 37 C.F.R. § 1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference....the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes. (Id. at 267, emphasis added).

Thus, *In re Moore* confirms the Stempel Doctrine, holding that in order to effectively remove a cited reference with a declaration under 37 C.F.R. § 1.131, an applicant need only show

that portion of his or her claimed invention that appears in the cited reference. Moreover, *In re Moore* stands for the proposition that when a cited reference discloses a claimed chemical compound either absent a utility or with a utility that is different from the one appearing in the claims at issue, a patent applicant can effectively swear back of that reference by simply showing prior possession of the claimed chemical compound. In other words, under this scenario, the patent applicant need not demonstrate that he or she had discovered a patentable utility for the claimed chemical compound prior to the effective date of the prior art reference.

While these cases discuss the ability to effectively swear back of the cited reference by way of a 131 declaration, Applicants submit that the same reasoning applies here, where the application claims priority back to a disclosure that predates the cited references. AF184971 discloses nothing more than a sequence which is homologous to a portion of SEQ ID NO: 75. Applicants demonstrated, by means of the disclosure in their provisional application filed September 10, 1998, that they were in possession of so much of the claimed invention, i.e. SEQ ID NO: 75, as disclosed in the AF184971 reference dated January 13, 2000. Thus, Applicants respectfully submit that the cited reference is not available as prior art, and request that the rejection under 35 U.S.C. §103 be withdrawn.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: May 5, 2005

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